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Primary care

Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials

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Abstract

Objective To determine the efficacy and tolerability of topical pimecrolimus and tacrolimus compared with other treatments for atopic dermatitis.

Design Systematic review and meta-analysis.

Data sources Electronic searches of the Cochrane Library, Medline, and Embase.

Study selection Randomised controlled trials of topical pimecrolimus or tacrolimus reporting efficacy outcomes or tolerability.

Data extraction Efficacy: investigators' global assessment of response; patients' global assessment of response; proportions of patients with flares of atopic dermatitis; and improvements in quality of life. Tolerability: overall rates of withdrawal; withdrawal due to adverse events; and proportions of patients with burning of the skin and skin infections.

Data synthesis 4186 of 6897 participants in 25 randomised controlled trials received pimecrolimus or tacrolimus. Both drugs were significantly more effective than a vehicle control. Tacrolimus 0.1% was as effective as potent topical corticosteroids at three weeks and more effective than combined treatment with hydrocortisone butyrate 0.1% (potent used on trunk) plus hydrocortisone acetate 1% (weak used on face) at 12 weeks (number needed to treat (NNT) = 6). Tacrolimus 0.1% was also more effective than hydrocortisone acetate 1% (NNT = 4). In comparison, tacrolimus 0.03% was more effective than hydrocortisone acetate 1% (NNT = 5) but less effective than hydrocortisone butyrate 0.1% (NNT = −8). Direct comparisons of tacrolimus 0.03% and tacrolimus 0.1% consistently favoured the higher strength formulation, but efficacy differed significantly between the two strengths only after 12 weeks' treatment (rate ratio 0.80, 95% confidence interval 0.65 to 0.99). Pimecrolimus was far less effective than betamethasone valerate 0.1% (NNT = −3 at three weeks). Pimecrolimus and tacrolimus caused significantly more skin burning than topical corticosteroids. Rates of skin infections in any of the comparisons did not differ.

Conclusions Both topical pimecrolimus and topical tacrolimus are more effective than placebo treatments for atopic dermatitis, but in the absence of studies that show long term safety gains, any advantage over topical corticosteroids is unclear. Topical tacrolimus is similar to potent topical corticosteroids and may have a place for long term use in patients with resistant atopic dermatitis on sites where side effects from topical corticosteroids might develop quickly. In the absence of key comparisons with mild corticosteroids, the clinical need for topical pimecrolimus is unclear. The usefulness of either treatment in patients who have failed to respond adequately to topical corticosteroids is also unclear.

Introduction

Atopic dermatitis is a common inflammatory skin disorder that affects 15-20% of children in developed countries,[1] and 1-3% of adults. The social and economic impact of this disorder is considerable, especially in severe cases, with patients experiencing intractable itch, loss of sleep, bleeding from the skin, and interference with most aspects of daily life.[2–4] In the United Kingdom, the annual cost of treating atopic dermatitis in children aged 1-5 years is £47m (1996 values) (currently $88m, €68m), with £30m spent by the NHS and £17m spent by affected families.[5]

Traditionally the treatment of atopic dermatitis has included the frequent use of emollients and the intermittent use of topical corticosteroids to control acute flares. Corticosteroids, although effective, may be associated with several local and systemic adverse events, such as thinning of the skin and adrenal gland suppression. Patients' fears about the safety profile of topical corticosteroids also have important implications for adherence to treatment, and knowledge on differentiating weak preparations from strong preparations is poor.[6 7]

Two new topical immunosuppressive treatments, pimecrolimus and tacrolimus, were developed to provide alternatives to topical corticosteroids without the associated adverse events. They work by inhibiting calcineurin in the skin, which regulates the activity of several transcription factors that control cell division and trigger the early stages of T cell activation. We undertook a systematic review and meta-analysis of all published randomised controlled trials of pimecrolimus and tacrolimus in atopic dermatitis to determine whether the drugs offer any advantages over existing treatments for atopic dermatitis, such as topical corticosteroids, in terms of efficacy, improved tolerability, and fewer short term or long term adverse effects.

Methods

We included randomised controlled trials that compared topical pimecrolimus or topical tacrolimus at a licensed therapeutic dose with vehicle or another active treatment (for example, topical corticosteroids) in patients with atopic dermatitis, and that reported efficacy outcomes or adverse events.

Outcome measures

For efficacy, we used the investigators' rating of the global degree of improvement. The trials used different scales to rate the degree of improvement. For pimecrolimus, we used the proportion of patients who were rated by the investigator as clear or almost clear as the primary outcome measure, whereas for the tacrolimus trials the primary outcome was the proportion of patients who achieved at least 90% improvement from baseline (defined as clear or excellent improvement in the trials).

Secondary outcome measures included patients' global assessments of feeling better or much better, the proportions of patients with flares of atopic dermatitis, and improvements in quality of life. We assessed tolerability to the drug by considering overall rates of withdrawal, withdrawal due to adverse events, and the proportions of patients with burning of the skin and skin infections.

Search strategy

Randomised controlled trials fulfilling the eligibility criteria were suitable for inclusion in our review, regardless of language or publication status. We systematically searched Medline, Embase, the Cochrane Skin Group specialised register, and the Cochrane central register of controlled trials to December 2004 using the search terms "pimecrolimus", "Elidel", "SDZ ASM 981", "tacrolimus", "Protopic", and "FK506". We also searched the reference lists of all retrieved trials along with the websites for the European Agency for the Evaluation of Medicinal Products and the US Food and Drug Administration.

Trial eligibility was determined by two authors (DMA, PD), who also independently extracted the data, which was checked by RG. Trials were rated for methodological quality (in duplicate by DMA and PD) using the Jadad scale and scored out of a maximum of five.[8]

Data synthesis

Not all of the trials reported on all the outcomes of interest. For each comparison and outcome we undertook separate meta-analyses. We grouped the topical corticosteroids on the basis of their potencies: mild (aclometasone dipropionate 0.1%, hydrocortisone acetate 1%) and potent (betamethasone valerate 0.1%, hydrocortisone butyrate 0.1%, triamcinolone acetonide 0.1%). We also stratified the analysis of efficacy data by the duration of treatment.

We summarised dichotomous data as rate ratios (relative risks) and combined these by using a random effects model.[9] Results are given with 95% confidence intervals. We also computed homogeneity statistics to test the agreement of the individual trial results with the combined meta-analytical summary.[10 11] Analyses were carried out in RevMan version 4.2.6.

Results

Overall, 25 randomised controlled trials met our inclusion criteria, totalling 6897 patients with atopic dermatitis (fig 1).[12–34] Table 1 details these trials. Eleven trials investigated the effects of pimecrolimus 1% cream applied twice daily; eight were vehicle controlled and three used an active comparator. The 11 trials included a total of 2688 participants consisting of infants (437), children (1222), and adults (1029) with atopic dermatitis of varying severity. One trial compared pimecrolimus and tacrolimus 0.03% directly in 141 children with moderate atopic dermatitis.[31] Fourteen trials investigated the effects of tacrolimus 0.1% ointment or tacrolimus 0.03% ointment applied twice daily; seven were vehicle controlled and seven used an active comparator. The 14 trials included a total of 4209 participants with moderate to severe atopic dermatitis, consisting of 2712 adults and 1497 children.

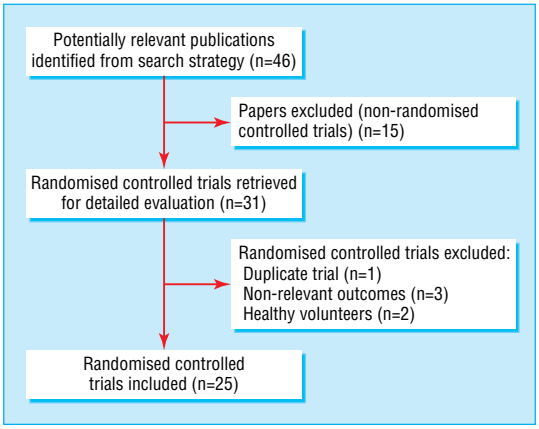

Fig 1 Flow of studies included in review

Vehicle controlled studies

Pimecrolimus 1% versus vehicle

Five trials (783 patients) reported on the proportion of patients clear or almost clear at three weeks.[12 13 15 18] Pimecrolimus was significantly more effective than vehicle (pooled rate ratio 2.72, 95% confidence interval 1.84 to 4.03; fig 2). The three trials that reported outcome after six weeks found that pimecrolimus remained significantly more effective (2.03, 1.50 to 2.74). Another trial (251 patients) found no significant difference between the proportions of patients clear or almost clear at six months (rate ratio 1.46, 0.98 to 2.19).[14] In three vehicle controlled trials (1156 patients), pimecrolimus resulted in significantly fewer patients with a flare of atopic dermatitis at six months (pooled rate ratio 1.92, 1.56 to 2.36).[14 16 17] At 12 months, pimecrolimus remained significantly more effective than vehicle at preventing flares (two trials: 1.84, 1.50 to 2.24). Both trials allowed use of a moderately potent topical corticosteroid as rescue medication and both showed significantly reduced rates of corticosteroid use at six months (1.82, 1.51 to 2.21) and 12 months (1.82, 1.52 to 2.18).[14 17]

Tacrolimus versus vehicle

One trial (136 children) directly compared tacrolimus 0.03%, tacrolimus 0.1%, and vehicle control, and reported on the proportion of children clear or achieving an excellent improvement (physician's global estimate of 90% improvement or better) at three weeks.[20] Tacrolimus 0.03% was significantly more effective than vehicle (rate ratio 2.13, 1.24 to 3.68), but response between tacrolimus 0.1% and vehicle did not differ significantly (1.57, 0.88 to 2.81). On the basis of the patients' global assessment of response as better or much better, both tacrolimus 0.03% and tacrolimus 0.1% were significantly more effective than vehicle (1.47, 1.06 to 2.04 and 1.76, 1.31 to 2.36, respectively). Three trials (656 patients) also reported on the same outcomes after 12 weeks' treatment and found that tacrolimus 0.03% and tacrolimus 0.1% were significantly more effective than vehicle (pooled rate ratios for proportion of patients clear or achieving excellent improvement 4.50, 2.91 to 6.96 and 5.62, 3.67 to 8.61, respectively; fig 3). Likewise, the pooled rate ratios for the patients' global assessment of response as better or much better were 3.31 (2.61 to 4.19) for tacrolimus 0.03% and 3.59 (2.65 to 4.88) for tacrolimus 0.1%.

Table 1 Characteristics of randomised controlled trials included in meta-analysis

Trial	No (age) of participants	Severity of atopic dermatitis	Intervention; control	Quality score[8]	Duration and blinding	Outcomes
Barba 2003[18]	114 infants, children, and young people (3 months to 18 years)	Mild to moderate facial eczema	Pimecrolimus 1% twice daily; vehicle	3/5	Three weeks DB followed by 24 weeks open label	IGA, pruritus, patient assessment
Eichenfield 2002[12]	198 children and young people (2-16 years)	Mild to moderate	Pimecrolimus 1% twice daily; vehicle	3/5	Six weeks DB followed by 20 weeks open label	IGA, EASI, pruritus, individual symptoms (erythema, induration or papulation, excoriation, lichenification)
Eichenfield 2002[12]	205 children and young people (2-16 years)	Mild to moderate	Pimecrolimus 1% twice daily; vehicle	3/5	Six weeks DB followed by 20 weeks open label	IGA, EASI, pruritus, individual symptoms (erythema, induration or papulation, excoriation, lichenification)
Ho 2003[13]	186 infants (2-23 months)	Mild to moderate	Pimecrolimus 1% twice daily; vehicle	3/5	Six weeks DB followed by 20 weeks open label	IGA, EASI, pruritus, individual symptoms (erythema, induration or papulation, excoriation, lichenification)
Kapp 2002[14]	251 infants (3-23 months)	Mild to severe	Pimecrolimus 1% twice daily; vehicle	4/5	12 months DB	Incidence of flares, IGA, topical corticosteroid requirement, pruritus, caregiver assessment, EASI
Kempers 2003[31]	141 children (2-17 years)	Moderate	Pimecrolimus 1% twice daily; tacrolimus 0.03% twice daily	3/5	Six weeks DB followed by 20 weeks open label	IGA, pruritus, formulation acceptability
Ling 2002[19]	49 adults and children (>10 years)	Moderate to severe	Pimecrolimus 1% four times daily; pimecrolimus 1% twice daily	2/5	Three weeks DB with crossover after seven days	IGA, EASI, pruritus, body surface area affected
Luger 2001[15]	130 adults	Moderate to severe	Pimecrolimus 0.05%, 0.2%, 0.6%, and 1% twice daily; vehicle or betamethasone-17-valerate 0.1%	3/5	Three weeks DB	EASI, IGA, pruritus
Luger 2004[33]	658 adults	Moderate to severe	Pimecrolimus 1% twice daily; triamcinolone acetonide 0.1% (trunk, limbs) hydrocortisone acetate 1% (face, neck, intertriginous areas)	3/5	12 months DB	EASI, IGA, skin infections, reaction at application site
Meurer 2002[16]	192 adults	Moderate to severe	Pimecrolimus 1% twice daily; vehicle	5/5	Six months DB	Topical corticosteroid requirement, incidence of flares, IGA, EASI, QoL score (DLQI and QoLIAD), pruritus
Wahn 2002[17]	713 children and young people (2-17 years)	Mild to severe	Pimecrolimus 1% twice daily; vehicle	5/5	12 months DB	Incidence of flares, IGA, topical corticosteroid requirement
Boguniewicz 1998[20]	136 children and young people (7-16 years)	Moderate to severe	Tacrolimus 0.03%, 0.1%, and 0.3% twice daily; vehicle	5/5	Three weeks DB	PGE, pruritus
Hanifin 1998[30]	33 children (3-6 years)	Moderate to severe	Tacrolimus 0.03% and 0.1% twice daily; vehicle	2/5	Three weeks DB	PGE (marked improvement or better)
Hanifin 2001[21]	205 adults	Moderate to severe	Tacrolimus 0.03% and 0.1% twice daily; vehicle	3/5	12 weeks DB	PGE, EASI, pruritus, individual symptoms (oedema, erythema, excoriation, lichenification, oozing, scaling)
Hanifin 2001[21]	218 adults	Moderate to severe	Tacrolimus 0.03% and 0.1% twice daily; vehicle	3/5	12 weeks DB	PGE, EASI, pruritus, individual symptoms (oedema, erythema, excoriation, lichenification, oozing, scaling)
Kang 1998[29]	26 adults	Moderate to severe	Tacrolimus 0.03%, 0.1%, and 0.3% twice daily; vehicle	2/5	Three weeks DB	PGE (marked improvement or better)
Kawashima 1997[27]	181 adults	Moderate to severe	Tacrolimus 0.1% twice daily; betamethasone valerate 0.12%	5/5	Three weeks DB	PGE, individual symptoms (erythema, swelling, papules, prurigo nodularis, infiltration, desquamation, erosion, encrustation, itching)
Nakagawa 1998[28]	143 adults	Moderate to severe	Tacrolimus 0.1% twice daily; aclometasone dipropionate 0.1%	1/5	One week DB	PGE (face and neck)
Pacor 2004[34]	30 children and adults (13-45 years)	Moderate to severe	Tacrolimus 0.1% twice daily; oral cyclosporin 3 mg/kg once daily	5/5	Six weeks DB	SCORAD, pruritus, erythema, adverse events
Paller 2001[22]	351 children (2-15 years)	Moderate to severe	Tacrolimus 0.03% and 0.1% twice daily; vehicle	3/5	12 weeks DB	PGE, EASI, pruritus, individual symptoms (oedema, erythema, excoriation, lichenification, oozing, scaling)
Reitamo 2002[23]	570 adults	Moderate to severe	Tacrolimus 0.03% and 0.1% twice daily; hydrocortisone butyrate 0.1%	5/5	Three weeks DB	mEASI, PGE
Reitamo 2002[24]	560 children	Moderate to severe	Tacrolimus 0.03% and 0.1% twice daily; hydrocortisone acetate 1%	5/5	Three weeks DB	mEASI, PGE
Reitamo 2003[32]	968 adults	Moderate to severe	Tacrolimus 0.1% twice daily; hydrocortisone butyrate 0.1% (trunk, extremities) hydrocortisone acetate 1% (head, neck)	5/5	24 weeks DB	mEASI, PGE
Reitamo 2004[26]	623 children	Moderate to severe	Tacrolimus 0.03% twice daily and once daily; hydrocortisone acetate 1%	4/5	Three weeks DB	mEASI, PGE, itch, quality of sleep
Ruzicka 1997[25]	162 adults	Moderate to severe	Tacrolimus 0.03%, 0.1%, and 0.3% twice daily; vehicle	4/5	Three weeks DB	PGE

DB=double blind; DLQI=dermatology life quality index; EASI=eczema area and severity index (mEASI=modified EASI); IGA=investigators' global assessment; PGE=physicians' global evaluation; QoL=quality of life; QoLIAD=quality of life index—atopic dermatitis; SCORAD=severity scoring of atopic dermatitis index.

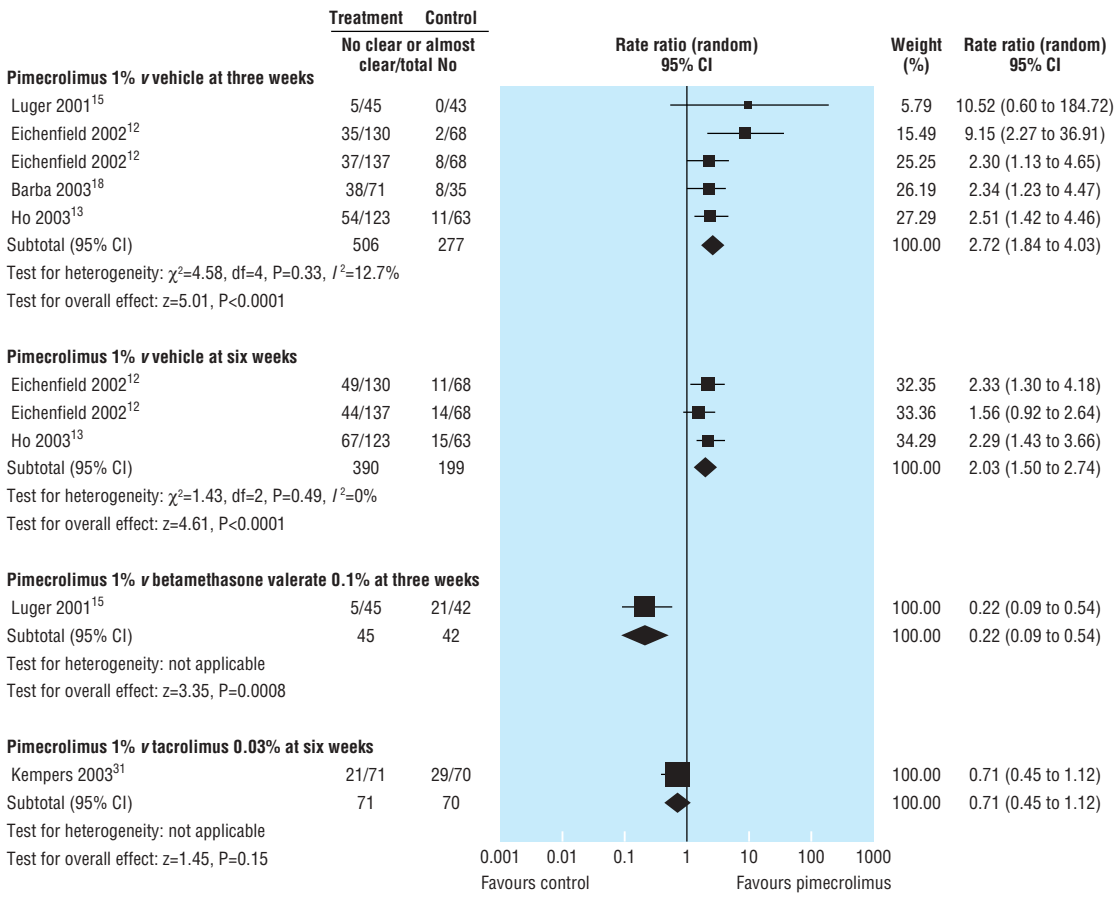

Fig 2 Investigators' global assessment of response (clear or almost clear) in trials comparing pimecrolimus 1% and control

Comparative efficacy of topical pimecrolimus

No published trials compared pimecrolimus 1% with mild corticosteroid.

Pimecrolimus 1% versus potent corticosteroid

One trial (87 patients) compared pimecrolimus 1% with betamethasone valerate 0.1% and reported on the proportion of patients clear or almost clear.[15] Betamethasone valerate 0.1% was significantly more effective than pimecrolimus 1% after three weeks' treatment (rate ratio 0.22, 0.09 to 0.54; fig 2).

Pimecrolimus 1% versus potent corticosteroid (trunk) and mild corticosteroid (face)

One trial (658 adults with moderate to severe atopic dermatitis) compared pimecrolimus 1% with a combined treatment regimen of triamcinolone acetonide 0.1% (trunk and limbs) and hydrocortisone acetate 1% (face, neck, and intertriginous areas).[33] On the basis of the proportions of patients moderately clear or better, the combined topical corticosteroid regimen was significantly more effective than pimecrolimus 1% after treatment for one week, three weeks, and six months, but treatment groups did not differ significantly at the end of treatment (12 months). A high level of attrition occurred in the pimecrolimus arm of this trial, with only 41% (135/328) of patients who received pimecrolimus 1% completing the study.

Pimecrolimus 1% versus tacrolimus 0.03%

One direct comparison of pimecrolimus 1% against tacrolimus 0.03% (141 children with moderate atopic dermatitis) found no significant difference in the proportion of children clear or almost clear at six weeks (0.71, 0.45 to 1.12).[31]

Pimecrolimus 1% four times daily versus pimecrolimus 1% twice daily

One crossover trial (49 patients with moderate to severe atopic dermatitis) found no significant difference in the proportion of patients clear or almost clear with four times daily versus twice daily application of pimecrolimus 1% cream at three weeks (0.96, 0.40 to 2.33).[19]

Comparative efficacy of topical tacrolimus

Tacrolimus versus mild topical corticosteroids

Two trials compared tacrolimus with hydrocortisone acetate 1% in 1183 children with moderate to severe atopic dermatitis.[24 26] Both tacrolimus 0.03% and tacrolimus 0.1% were significantly more effective than hydrocortisone acetate 1% on the basis of the proportion of patients clear or achieving excellent improvement at three weeks; the corresponding rate ratios were 2.56 (1.95 to 3.36) and 3.05 (2.12 to 4.40). One further trial compared tacrolimus 0.1% with aclometasone dipropionate 0.1% (mild corticosteroid) in 143 patients with atopic dermatitis affecting the face and neck.[28] Tacrolimus 0.1% was significantly more effective than aclometasone dipropionate 0.1% for treating facial atopic dermatitis (rate ratio for proportion of patients achieving at least marked improvement (>75%) at one week 3.94, 2.21 to 7.00).

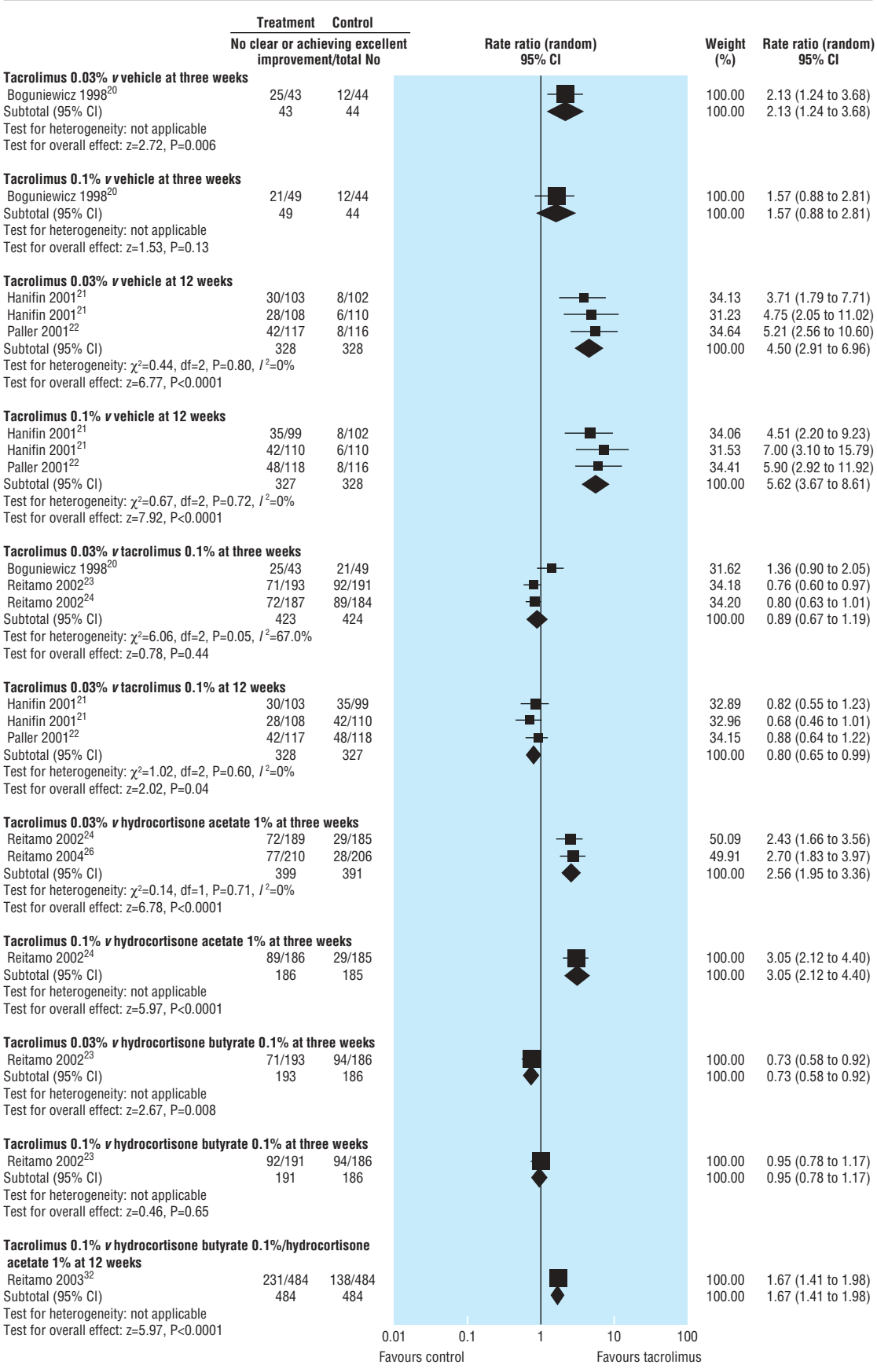

Fig 3 Investigators' global assessment of response (clear or excellent improvement) in trials comparing tacrolimus (0.03% and 0.1%) and control

Tacrolimus versus potent topical corticosteroids

One trial (570 adults with moderate to severe atopic dermatitis) compared tacrolimus (0.03% and 0.1%) with hydrocortisone butyrate 0.1% (potent corticosteroid) and reported on the proportions of patients clear or achieving an excellent improvement at three weeks.[23] Tacrolimus 0.03% was significantly less effective than hydrocortisone butyrate 0.1% (0.73, 0.58 to 0.92), whereas tacrolimus 0.1% was as effective (0.95, 0.78 to 1.17).

Two trials compared tacrolimus 0.1% with potent topical corticosteroids (betamethasone valerate 0.1%, hydrocortisone butyrate 0.1%) and reported on the proportions of patients achieving at least marked improvement (>75%) at three weeks.[23 27] Tacrolimus 0.1% was as effective as the potent topical corticosteroids (pooled rate ratio 1.08, 0.97 to 1.21).

Tacrolimus versus potent corticosteroid (trunk) and mild corticosteroid (face)

One trial (968 adults with moderate to severe atopic dermatitis) compared tacrolimus 0.1% with a combined treatment regimen of hydrocortisone butyrate 0.1% (trunk and extremities) plus hydrocortisone acetate 1% (head and neck).[32] At 12 weeks, tacrolimus 0.1% was significantly more effective than the combined topical corticosteroid regimen on the basis of the proportions of patients clear or achieving an excellent improvement (1.67, 1.41 to 1.98).

Tacrolimus 0.03% versus tacrolimus 0.1%

Six trials (1502 patients) directly compared tacrolimus 0.03% with tacrolimus 0.1%.[20–24] Three of the trials reported on the proportions of patients clear or achieving an excellent improvement at three weeks and found no significant difference in response between strengths of tacrolimus (pooled rate ratio 0.89, 0.67 to 1.19; fig 3). At 12 weeks in the remaining three trials, however, tacrolimus 0.1% was significantly more effective than tacrolimus 0.03% (0.80, 0.65 to 0.99). On the basis of the participants' global assessment of response of better or much better, response did not differ significantly between strengths: three weeks (0.84, 0.69 to 1.00) and 12 weeks (0.93, 0.83 to 1.03).

Quality of life

Information on quality of life was patchy, with a lack of common outcome measures. In two trials that compared pimecrolimus with vehicle, the parent's index of quality of life in atopic dermatitis was completed by the parents of a subset of patients (children aged 2-8 years); those children who received pimecrolimus were judged by their parents to have a significantly improved quality of life compared with those receiving vehicle.[35] In one trial (192 adults with moderate to severe atopic dermatitis), patients receiving pimecrolimus had a significantly improved quality of life compared with those receiving vehicle, assessed using both the quality of life index—atopic dermatitis and the dermatology life quality index.[16]

In three trials (985 patients), significant improvements in overall quality of life were found separately for infants, children, and adults treated with tacrolimus (0.03% and 0.1%) compared with vehicle.[36] Quality of life was assessed using the dermatology life quality index in adults, the children's dermatology life quality index, and a modified version of this instrument for toddlers. Tacrolimus 0.1% also resulted in a significantly greater improvement in quality of life than tacrolimus 0.03% in adults, but no significant differences were found between strengths in infants or children. We did not identify any quality of life assessments for participants treated with pimecrolimus or tacrolimus and compared directly with a topical corticosteroid.

Withdrawal from treatment

Significantly more patients withdrew from treatment with vehicle than with pimecrolimus 1% or tacrolimus 0.03% or 0.1% (table 2). Most patients dropped out as a result of lack of response associated with the vehicle control. Rates of withdrawals due to adverse events did not differ significantly between pimecrolimus 1% and vehicle, but were significantly higher with tacrolimus 0.03% and tacrolimus 0.1% (pooled rate ratios 0.50, 0.30 to 0.84 and 0.47, 0.28 to 0.80, respectively).

Rates of withdrawals due to adverse events did not differ significantly any of the comparisons of pimecrolimus or tacrolimus (0.03% and 0.1%) with topical corticosteroids. Direct comparisons of tacrolimus 0.03% and tacrolimus 0.1% showed no significant differences in withdrawals between strengths of tacrolimus (pooled rate ratio for overall withdrawals 0.75, 0.49 to 1.14 and for withdrawals due to adverse effects 0.99, 0.59 to 1.64).

Adverse effects

The most common adverse effects reported related to skin irritation and skin burning. Pimecrolimus 1% and vehicle did not differ significantly in the incidence of skin burning (pooled rate ratio obtained from six trials was 0.87, 0.70 to 1.09), but the rate of skin burning was significantly higher with pimecrolimus 1% than with betamethasone valerate 0.1% (5.26, 1.92 to 14.30) or a combined regimen of triamcinolone acetonide 0.1% and hydrocortisone acetate 1% (2.38, 1.66 to 3.40).

Tacrolimus 0.03% and tacrolimus 0.1% were significantly more likely to cause skin burning than vehicle (pooled rate ratios 1.89, 1.43 to 2.50 and 2.08, 1.35 to 3.18, respectively). Both tacrolimus 0.03% and tacrolimus 0.1% were significantly more likely to cause skin burning than were mild or potent topical corticosteroids (table 2). The incidence of skin infections was not significantly different in any of the comparisons of pimecrolimus or tacrolimus with control (active or vehicle). None of the trials reported on key adverse effects such as thinning of skin or adrenal gland suppression.

Discussion

Tacrolimus 0.1% is as effective as potent topical corticosteroids and more effective than mild topical corticosteroids, such as hydrocortisone acetate 1%, for treating atopic dermatitis. This means that topical tacrolimus may be useful for resistant atopic dermatitis at sensitive sites such as the face, where the use of more potent topical steroids carries a high risk of thinning of the skin and telangiectasia. Tacrolimus 0.1% may also be useful for patients who depend on the constant use of potent steroids, although it would be helpful to see trial evidence on how effective it is in such a subgroup of treatment "failures."

Pimecrolimus has been found to be less effective than betamethasone valerate 0.1%, a commonly used potent topical corticosteroid. The efficacy of pimecrolimus compared with less potent topical corticosteroids is not known. In practice, pimecrolimus is being aimed at patients with mild atopic dermatitis, yet this is being done in the absence of randomised controlled trials that compare it with existing therapy for such a group—that is, short bursts of 1% hydrocortisone to treat acute flares. Pimecrolimus prevented more flares than vehicle, but it remains to be seen whether the early use of mild topical steroids may be as effective. In the absence of such key comparisons, it is unclear as to what role, if any, pimecrolimus has for atopic dermatitis.

The main reason for developing new drugs as an alternative to topical steroids is to overcome possible side effects from steroids, such as thinning of the skin or adrenal gland suppression. We found no clear evidence that these newer, more expensive

Table 2 Withdrawals and adverse events in trials of pimecrolimus and tacrolimus for treating atopic dermatitis

Adverse effect	Crude rate	No of studies	Pooled relative risk (95% CI)	Test for homogeneity	
				P value	I^2 (%)
Pimecrolimus 1% *v* vehicle:					
Withdrawal (any reason)	273/1211 *v* 259/622	7	0.49 (0.38 to 0.64)*	0.042	54.1
Withdrawal (side effects)	9/408 *v* 15/275	4	0.46 (0.20 to 1.06)	0.887	0
Bacterial skin infections	98/899 *v* 84/443	4	0.67 (0.28 to 1.60)	0.042	63.5
Viral skin infections	76/776 *v* 23/380	3	1.53 (0.78 to 2.99)	0.191	39.6
Skin burning	204/1166 *v* 131/579	6	0.87 (0.70 to 1.09)	0.257	24.6
Pimecrolimus 1% *v* potent corticosteroid (betamethasone valerate 0.1%):					
Withdrawa (any reason)	19/43 *v* 7/45	1	2.17 (0.60 to 7.69)	—	—
Withdrawal (side effects)	1/43 *v* 3/45	1	2.78 (0.30 to 25.0)	—	—
Skin burning	1/43 *v* 2/45	1	5.26 (1.92 to 14.3)*	—	—
Pimecrolimus 1% *v* triamcinolone acetonide 0.1% (trunk and limbs) and hydrocortisone acetate 1% (face and neck):					
Skin infections (any)	69/328 *v* 80/330	1	0.87 (0.65 to 1.15)	—	—
Bacterial skin infections	39/328 *v* 43/330	1	0.91 (0.61 to 1.37)	—	—
Fungal skin infections	1/328 *v* 4/330	1	0.25 (0.03 to 2.24)	—	—
Viral skin infections	16/328 *v* 26/330	1	0.62 (0.34 to 1.13)	—	—
Skin burning	85/328 *v* 36/330	1	2.38 (1.66 to 3.40)*	—	—
Tacrolimus 0.1% *v* vehicle:					
Withdrawa (any reason)	81/430 *v* 238/426	5	0.35 (0.27 to 0.46)*	0.22	30.6
Withdrawal (side effects)	19/430 *v* 42/426	5	0.47 (0.28 to 0.80)*	0.714	0
Skin infections	27/327 *v* 18/330	3	1.48 (0.83 to 2.65)	0.53	0
Skin burning	187/430 *v* 92/426	5	2.08 (1.35 to 3.18)*	0.010	69.9
Tacrolimus 0.03% *v* vehicle:					
Withdrawa (any reason)	93/425 *v* 238/426	5	0.40 (0.33 to 0.48)*	0.81	0
Withdrawal (side effects)	20/425 *v* 42/426	5	0.50 (0.30 to 0.84)*	0.800	0
Skin infections	27/327 *v* 32/330	3	0.85 (0.52 to 1.39)	0.72	0
Skin burning	173/425 *v* 92/426	5	1.89 (1.43 to 2.50)*	0.202	32.9
Tacrolimus 0.1% *v* mild corticosteroid (hydrocortisone acetate 1%):					
Withdrawa (any reason)	13/186 *v* 20/185	1	0.65 (0.33 to 1.27)	—	—
Withdrawal (side effects)	3/186 *v* 4/185	1	0.75 (0.17 to 3.33)	—	—
Skin infections	4/186 *v* 4/185	1	0.99 (0.25 to 3.85)	—	—
Skin burning	38/186 *v* 13/185	1	2.94 (1.61 to 5.26)*	—	—
Tacrolimus 0.1% *v* potent corticosteroid (betamethasone valerate 0.1%, hydrocortisone butyrate 0.1%):					
Withdrawa (any reason)	33/283 *v* 25/275	2	1.32 (0.80 to 2.13)	0.822	0
Withdrawal (side effects)	8/191 *v* 3/186	1	2.56 (0.70 to 10.0)	—	—
Skin infections	6/92 *v* 5/89	1	1.16 (0.37 to 3.70)	—	—
Skin burning	138/283 *v* 27/275	2	4.76 (3.33 to 7.14)*	0.362	4.9
Tacrolimus 0.1% *v* hydrocortisone butyrate 0.1% (trunk and extremities) and hydrocortisone acetate 1% (face):					
Withdrawa (any reason)	124/488 *v* 204/487	1	0.61 (0.51 to 0.73)*	—	—
Withdrawal (side effects)	10/488 *v* 16/487	1	0.63 (0.29 to 1.37)	—	—
Skin infections	18/488 *v* 21/487	1	0.86 (0.46 to 1.59)	—	—
Skin burning	259/488 *v* 67/487	1	3.85 (3.03 to 5.00)*	—	—
Tacrolimus 0.03% *v* mild corticosteroid (hydrocortisone acetate 1%):					
Withdrawa (any reason)	42/399 *v* 61/392	2	0.71 (0.35 to 1.43)	0.022	56.8
Withdrawal (side effects)	11/399 *v* 10/392	2	1.09 (0.46 to 2.56)	0.529	0
Skin infections	12/399 *v* 10/392	2	1.18 (0.51 to 2.70)	0.157	36
Skin burning	85/399 *v* 43/392	2	1.96 (1.25 to 3.13)*	0.203	35.0
Tacrolimus 0.03% *v* potent corticosteroid (hydrocortisone butyrate 0.1%):					
Withdrawa (any reason)	22/193 *v* 17/186	1	1.03 (0.58 to 1.82)	—	—
Withdrawal (side effects)	7/193 *v* 3/186	1	0.74 (0.17 to 3.23)	—	—
Skin burning	87/193 *v* 24/186	1	3.45 (2.33 to 5.26)*	—	—
Tacrolimus 0.1% *v* tacrolimus 0.03%:					
Withdrawa (any reason)	96/807 *v* 136/807	7	0.75 (0.49 to 1.14)	0.024	58.9
Withdrawal (side effects)	30/807 *v* 30/807	7	0.99 (0.59 to 1.64)	0.556	0
Skin infections	22/513 *v* 38/517	4	0.60 (0.35 to 1.02)	0.367	5.2
Skin burning	338/807 *v* 295/807	7	1.14 (0.95 to 1.35)	0.075	47.6
Tacrolimus 0.1% *v* oral cyclosporin 3mg/kg:					
Skin burning	4/15 *v* 0/15	1	9.00 (0.53 to 153.79)	—	—

*P<0.05.

products offer such an advantage when compared with standard practice. Other studies have suggested that skin thinning is not a problem with these newer agents.[37 38] One preliminary randomised controlled trial of pimecrolimus applied to normal skin for four weeks found no thinning of the skin.[37] Such a study is, however, difficult to generalise to people with atopic dermatitis who apply preparations over the course of a year. A non-randomised prospective study of 119 participants that compared 0.1% topical tacrolimus with "conventional steroid based therapy" and normal controls found no evidence of decreased

skin collagen synthesis or skin thinning in the tacrolimus group as measured by ultrasonography at one year.[38] Skin collagen synthesis was also not decreased with conventional topical steroids, although a minor degree of skin thinning was found (mean decreased thickness of 8.2% compared with baseline); its clinical significance is difficult to interpret.

Strengths and limitations of the review

In contrast to an earlier review that identified 16 studies,[39] we examined 25 clinical trials, using a wider range of clinically relevant outcome measures, and focused on direct comparisons with other active treatments, rather than making indirect inferences from placebo controlled trials.

One limitation of our systematic review is that our analyses of rates of withdrawals and adverse events were based on data pooled from trials of different durations. Some caution is therefore needed in their interpretation. Other potential sources of heterogeneity in the results are the patient population (infants, children, adults), the severity of the disease, and the choice of topical corticosteroid. The use of investigators' global assessments of response to treatment also causes some concern. Despite such assessments of response to treatment being widely used as outcome measures in clinical trials of atopic dermatitis, further research is needed to fully determine their validity, reliability, and sensitivity to change.[40 41]

Recommendations for future research to inform clinical practice

Our systematic review shows that there is little evidence to help deal with the clinically important questions of how pimecrolimus and tacrolimus compare for efficacy, side effects, tolerability, and cost with existing optimal treatments, such as short bursts of topical corticosteroids for flare-ups of disease followed by periods of rest using only emollients. Although some comparative data are available for tacrolimus to inform practice, the clinical role of pimecrolimus is uncertain owing to a lack of relevant comparative data. The lack of key comparative data highlights deficiencies in the current licensing systems for medicines in Europe and the United States, which require only evidence of efficacy and safety above placebo and vehicle, thus allowing more new drugs to reach the market. This leaves doctors, commissioners, and the public confused about how and when to use such new drugs in relation to standard practice.

Pragmatic randomised controlled trials lasting at least 12 months are needed to compare tacrolimus, pimecrolimus, and 1% hydrocortisone acetate in children and adults with mild to moderate atopic dermatitis. Outcome data should include clearing capacity, relapse, quality of life, adverse events (including skin thinning), and costs. In particular, it seems important to determine how well these agents work in people who fail to respond adequately to topical corticosteroids, given that they may be used as second line agents.[42] Experience of long term use of topical pimecrolimus and tacrolimus is limited and the risk of rare but more serious adverse effects remains uncertain. Further long term surveillance of these agents is needed, given concerns about the theoretical risk of visceral and skin cancers from preclinical studies in animals.[43]

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What is already known on this topic

Atopic dermatitis affects 15-20% of children in developed countries

Topical corticosteroids and emollients have been the mainstay of therapy

Topical pimecrolimus and tacrolimus have been developed as alternative treatments

What this study adds

Tacrolimus 0.1% is as effective as potent corticosteroids for treating atopic dermatitis and more effective than mild preparations such as hydrocortisone acetate 1%

Pimecrolimus is less effective than potent corticosteroids; it has not been compared with mild corticosteroids

Both agents caused more burning of the skin than topical corticosteroids, but no differences were observed in rates of skin infections

Ethical approval: Not required.

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